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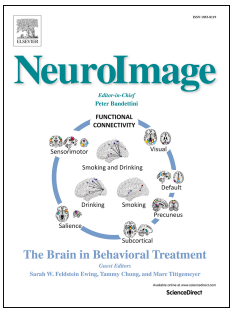

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High detection sensitivity with antibody-based PET radioligand for amyloid beta in brain

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Abstract

PET imaging of amyloid-beta (Aβ) deposits in brain has become an important aid in Alzheimer's disease diagnosis, and an inclusion criterion for patient enrolment into clinical trials of new anti-Aβ treatments. Available PET radioligands visualizing Aβ bind to insoluble fibrils, i.e. Aβ plaques. Levels of prefibrillar Aβ forms, e.g. soluble oligomers and protofibrils, correlate better than plaques with disease severity and these soluble species are the neurotoxic form of Aβ leading to neurodegeneration. The goal was to create an antibody-based radioligand, recognizing not only fibrillary Aβ, but also smaller and still soluble aggregates. We designed and expressed a small recombinant bispecific antibody construct, di-scFv 3D6-8D3, targeting the Aβ N-terminus and the transferrin receptor (TfR). Natively expressed at the blood-brain barrier (BBB), TfR could thus be used as a brain-blood shuttle. Di-scFv 3D6-8D3 bound to Aβ1-40 with high affinity and to TfR with moderate affinity. Di-scFv [^{124}I]3D6-8D3 was injected in two transgenic mouse models overexpressing human Aβ and wild-type control mice and PET scanned at 14, 24 or 72 h after injection. Di-scFv [^{124}I]3D6-8D3 was retained in brain of transgenic animals while it was cleared from wild-type lacking Aβ. This difference was observed from 24 h onwards, and at 72 h, 18 months old transgenic animals, with high load of Aβ pathology, displayed SUVR of 2.2-3.5 in brain while wild-type showed ratios close to unity. A subset of the mice were also scanned with [^{11}C]PIB. Again wt mice displayed ratios of unity while transgenes showed slightly, non-significantly, elevated SUVR of 1.2, indicating improved sensitivity with novel di-scFv [^{124}I]3D6-8D3 compared with [^{11}C]PIB. Brain concentrations of di-scFv [^{124}I]3D6-8D3 correlated with soluble Aβ ($p < 0.0001$) but not with total Aβ, i.e. plaque load ($p = 0.34$).

We have successfully created a small bispecific antibody-based radioligand capable of crossing the BBB, subsequently binding to and visualizing intrabrain Aβ *in vivo*. The radioligand displayed better sensitivity compared with [^{11}C]PIB, and brain concentrations correlated with soluble neurotoxic Aβ aggregates.

Keywords:

Alzheimer's disease; amyloid beta; PET; antibody-based radioligand; transferrin receptor; brain